REMARKS

Upon entry of the present amendments, claims 7-10, 13-15, 36, 37, and 39-50 will be pending. Claims 7, 8, 13, 15 and 37 have been amended. Support for the amendments can be found throughout the specification, for example, at page 5, lines 29-30; page 9, lines 1-5; page 20, lines 25-31; page 25, lines 15-27; and Tables 1 and 2. In particular, the amendments to claim 13 are supported in the specification, e.g., at page 9, lines 1-8, and at page 20, line 3. Applicants have also added new claims 40-49, which are supported, for example, at page 20, lines 25-31; page 25, lines 15-27, page 27, lines 1-30; and in Fig. 7. Applicants have canceled claims 1-6, 11-12, 16-35, and 38 without prejudice. Thus, the amendments and new claims add no new matter.

Restriction/Election

In response to applicants' election of Group II with traverse in the reply submitted on September 24, 2007, the Office maintained that claims 24 and 26-32 are withdrawn as being directed to non-elected inventions. Applicants have canceled these claims without prejudice.

Information Disclosure Statement

Applicants thank the Office for considering the references cited in the Information Disclosure Statements (IDSs) submitted on September 8, 2004 and September 24, 2007. As requested, included with this reply are replacement copies of the non-patent references cited in the IDS filed on September 8, 2004.

Drawings

The Office objected to Figure 8 as allegedly illegible. Applicants have submitted herewith a replacement sheet for Figure 8.

35 U.S.C. § 112, Second Paragraph

The Office rejected claims 13-16 as allegedly indefinite on two grounds.

First, according to the Office (Office Action at page 4):

> The teachings of the art indicate that a pseudovirus is a virus incorporating the envelope protein of a different virus ... Further, the specification (page 9) teaches that the pseudovirus is produced through the expression of the chimeric envelope protein of the invention in a cell also expressing the packing construct LGRNL, which encodes a VSV G protein. Burns, supra., page 8034 ... it is not clear what is meant in the claims by reference to the pseudovirus. It is not clear if the resulting viral particles require the presence of a different viral envelope protein in the place of, or in combination with, the chimeric envelope protein, or if the chimeric envelope protein is considered by the Applicant to serve as a foreign envelope protein.

Applicants do not agree with this rejection. However, for the purpose of expediting prosecution of this application, applicants have amended claim 13 to simplify and clarify as discussed in more detail below with respect to the Section 112, first paragraph, discussion. Applicants have also cancelled claim 16. Thus, applicants submit that claims 13-15 are sufficiently clear.

For example, applicants have deleted the term "pseudovirus" from claim 13. Applicants have also added additional steps to more clearly state how to obtain a retrovirus with an altered tropism. Hence, there is nothing indefinite about this claim. As claims 14 and 15 depend from claim 13, they are also not indefinite for at least the same reasons. Withdrawal of this rejection is respectfully requested.

Second, the Office states (at page 5):

> .. the claims are also ejected [sic] under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. In particular, the teachings of the application, and the understanding of what comprises a pseudotype virus in the art, indicates that such a virus is not made merely through the introduction of a mutation into a viral envelope protein in a viral genome.

Applicants respectfully disagree, but have amended claim 13 as discussed above for the purpose of expediting prosecution of this application. Claim 13 now recites introducing a nucleic acid molecule containing a nucleic acid sequence encoding a chimeric envelope protein (e.g., the nucleic acid molecule of claim 7) into a packaging cell, maintaining the packaging cell

under conditions such that a retrovirus is produced; and harvesting the retrovirus from the packaging cell, thereby producing a retrovirus having an altered retroviral tropism. As set forth above, such is precisely how a retrovirus, i.e., a virus that expresses a chimeric envelope protein, can be produced. Thus, claim 13, as well as claims 14 and 15 depending from it, are definite. As a result, applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 112, First Paragraph

The Office rejected claims 13-16 as allegedly failing to comply with the written description requirement. At page 5 of the Office Action, the Office states:

> This is a New Matter rejection ... Claim 13 is treated as representative. This claim has been amended to read on a method for altering viral tropism comprising introducing into the genome of a retrovirus a nucleic acid encoding a retroviral ecotropic envelope protein modified to include a peptide ligand as described in claim 7, and thereby producing a pseudovirus ... The application discloses only the production of a pseudovirus comprising the introduction into a cell of a nucleic acid encoding the chimeric envelope protein and a packaging construct such as is disclosed on page 9 of the application.

Applicants respectfully disagree and traverse for the reasons stated below.

First, applicants respectfully note that a method of altering retroviral tropism was recited in original claims 13-16, which are supported by the specification as filed, e.g., at page 2, lines 18-21. These claims were amended to depend from claim 7 in the Preliminary Amendment submitted on September 24, 2007, but otherwise recite the same subject matter. Accordingly, claims 13-16 do not contain new matter.

Second, applicants disagree with the Office's assertion that, because the specification describes introducing a nucleic acid molecule and a packaging construct into cells, there is no written description for introducing the nucleic acid molecule into the genome of a virus. On the other hand, for the purpose of moving this application forward, applicants have amended claim 13 to recite a method of altering retroviral tropism by introducing a nucleic acid molecule containing a nucleic acid sequence, e.g., encoding a chimeric Murine Leukemia Virus (MLV) ecotropic envelope protein having a heterologous short peptide ligand inserted therein, into a packaging cell, thereby producing a retrovirus having altered tropism.

It is well known in the art that viruses are not self-replicating, and viral particles containing the viral genome are assembled, i.e., packaged, in host cells. Thus, to produce a viral particle including a nucleic acid sequence of interest, a nucleic acid molecule, e.g., a vector, containing the nucleic acid sequence must be introduced into host cells, e.g., packaging cells. For example, a packaging cell can express some of the viral proteins necessary for making a virus, e.g., gag and pol. Packaging constructs, e.g., viral vectors, containing other components, e.g., a gene of interest, a gene for the envelope protein, a selectable marker, or viral enhancer/promoter sequences, can be transfected into a packaging cell line to produce a virus. Various methods, constructs and packaging cell lines for making wild-type, recombinant, or other retroviruses were known in the art at the time of filing. As MPEP 2163(II)(A)(2) states: "Information that is well known in the art need not be described in detail in the specification." In any event, as the Office acknowledges (at page 5, paragraph 9), the specification does provide descriptions of these methods and tools (e.g., at page 9, lines 1-7; and page 19, line 12 to page 20, line 2).

Applicants would also like to direct the Office to the method sections of the various references cited in this Office Action (see, e.g., Wu et al., Virology, 2000, 269:7-17 and Burns et al., Proc. Natl. Acad. Sci, 1993, 90:8033-8037) for further examples of methods and tools known in the art.

Thus, skilled practitioners, in view of the knowledge in the art and descriptions in the specification, would have recognized that applicants had possession of the claimed method. Accordingly, claim 13 and its dependent claims 14 and 15 do not contain new matter or lack written description. Withdrawal of this rejection is respectfully requested.

35 U.S.C. § 102 (b)

The Office rejected claims 7, 8, 10, 11, 35-37, and 39 as allegedly anticipated by Wu et al., Virology, 2000, 269:7-17 ("Wu"). To support this rejection, the Office states at pages 6-7:

> Wu discloses that an RGD peptide ligand was inserted into a site in an ecotropic MLV envelope protein where the peptide was flanked on either side by at least one cysteine residue ... the reference teaches that the viral particles comprising

one of the mutants meeting the limitations of the present claims (wherein the peptide ligand was inserted between residues 78 and 79 of the wild-type envelope protein) was capable of infecting murine cells.

Applicants respectfully disagree, but have amended claims 7 and 8, and canceled claims 11 and 35, for the purpose of expediting prosecution of the application. The claims are now drawn to an isolated nucleic acid molecule (claim 7) or a vector (claim 8) comprising a nucleic acid sequence encoding a chimeric envelope protein comprising an MLV ecotropic envelope protein with a heterologous short peptide ligand inserted within the N-terminal region or the variable region VRA of the extracellular domain (SU) of the MLV ecotropic envelope protein, such that a retroviral particle comprising the chimeric envelope protein is capable of infecting a human cell, but not a mouse cell. Wu fails to disclose such nucleic acid molecule and vector.

While Wu discloses nucleic acid molecules and vectors containing nucleic acid sequences encoding chimeric MLV envelope proteins, it fails to disclose viruses expressing these chimeric envelope proteins that are capable of infecting human cells, but not mouse cells. In fact, while some of the viruses disclosed in Wu retained the ability to infect mouse cells (see the Abstract), none were able to infect the M21 human melanoma cell line (see, e.g., page 14, right column, last paragraph). Thus, as Wu fails to teach every element of claim 7 and 8, it does not anticipate the claims. Neither does it anticipate claims 10, 36, 37 and 39, and new claims 40-44, all of which depend from claim 7 or 8. Withdrawal of this rejection is respectfully requested.

The Office next rejected claims 7, 8, 35-37, and 39 as allegedly anticipated by U.S. Pat. No. 6, 132,731 ("Kingsman). According to the Office (at page 7): "Kingsman teaches a nucleic acid encoding a chimeric ecotropic MLV envelope protein into which a RGD peptide ligand flanked by cysteines has been inserted. Columns 7-8." Applicants respectfully disagree. However, for the purpose of expediting prosecution of the application, applicants have amended claims 7 and 8 as described above, and canceled claim 35. Kingsman does not teach the nucleic acid molecule recited in claim 7 or the vector recited in claim 8.

In particular, Kingsman fails to teach an isolated nucleic acid molecule or a vector comprising a nucleic acid sequence encoding a chimeric MLV envelope, such that a retroviral

particle comprising the chimeric envelope protein is capable of infecting a human cell, but not a mouse cell. Instead, Kingman discloses viruses expressing chimeric MLV envelope proteins that infect mouse cells (see, e.g., Tables 1 and 2), which is the opposite of what the present claims recite. Therefore, the reference does not anticipate claim 7 or 8, or their dependent claims 36, 37 and 39. As new claims 40-44 also depend from claim 7 or 8, they are not anticipated. Applicants respectfully request that the Office withdrawal this rejection.

35 U.S.C. § 102(e)

The Office rejected claims 7, 8, 35, 37 and 38 as allegedly anticipated by U.S. Pat. No. 6,448,390 ("Albritton"). To support this rejection, the Office states (at pages 7-8): "Albritton teaches nucleic acids (and vectors comprising such) encoding mutated envelope proteins of an ecotropic MLV comprising an insertion between amino acid residues 6 (serine) and 7 (proline) the cyclic nonapeptide CDCRGDCFC as a peptide ligand. Columns 41-42." Applicants respectfully disagree, but for the purpose of expediting prosecution of the application, have amended claims 7 and 8 as set forth above, and cancelled claims 35 and 38. Albritton does not teach every element recited in these claims.

Like Wu and Kingsman, Albritton fails to disclose a nucleic acid molecule or a vector comprising a nucleic sequence comprising a nucleic acid sequence encoding a chimeric envelope protein including a MLV ecotropic envelope protein, such that a retroviral particle comprising the chimeric envelope protein is capable of infecting a human cell, but not a mouse cell. Instead, Albritton clearly describes viruses expressing chimeric envelope proteins that infect mouse cells (see, e.g., Fig. 7). The Office has not pointed to anything in Albritton that describes the presently claims nucleic acid molecules or vectors. Accordingly, Albritton does not anticipate either claim 7 or 8, or any of their dependent claims, claim 37 and new claims 40-44. Withdrawal of this rejection is respectfully requested.

35 U.S.C § 103

The Office rejected claims 9-11 and 13-16 as allegedly obvious over Albritton. The Office states (at pages 8-9):

> Reference to the pseudovirus in the claim is interpreted as including any virus particle comprising a non-native viral envelope protein, such as a modified version of the virus' own envelope protein ... The reference teaches a nucleic acid encoding a chimeric ecotropic MLV envelope protein as described by the present claims, and indicates that retroviral particles expressing the chimeric protein are capable of infecting and thereby delivering genes to targeted human cells ... Thus, the claimed vectors and methods would have been obvious to those of ordinary skill in the art based on the teachings of the reference.

Applicants respectfully disagree and traverse for the reasons stated below. Claims 9-11 and 13-16 depend from claims 8 and 7, respectively, both of which have been amended as discussed above. Claims 11 and 16 have been canceled. Accordingly, these claims recite an isolated nucleic acid molecule or a vector comprising a nucleic acid sequence encoding a chimeric envelope protein including a MLV ecotropic envelope protein with a heterologous short peptide ligand inserted within the N-terminal region or the VRA region of the SU of the MLV ecotropic envelope protein, such that a retroviral particle comprising the chimeric envelope protein is capable of infecting a human cell, but not a mouse cell.

As set forth above, Albritton fails to disclose the nucleic acid molecule of claim 7 or the vector of claim 8. Accordingly, the Office fails to present a *prima facie* case of obviousness. Even if the Office could make such a *prima facie* case, it is overcome by Albritton's disclosure of viruses that are capable of infecting mouse cells, which teaches away from applicants' claims reciting viruses not capable of infecting mouse cells. Further, in view of Albritton's disclosure, it was surprising that viruses expressing applicants' chimeric envelope proteins are able to infect human cells, but not mouse cells. Thus, claims 9-10 and 13-15, would not have been obvious in view of Albritton, and applicants respectfully request withdrawal of this rejection.

The Office next rejected claims 9-11, 13-15 and 39 as allegedly obvious over Kingsman in view of U.S. Pat. No. 5,985,655 ("Anderson"). To support this rejection, the Office states (at pages 10-11):

> ...while [Kingsman] teaches the retroviral vectors, it does not teach that the vectors encode the chimeric envelope protein. Anderson also teaches retroviral viral particles comprising chimeric envelope proteins changing the viral tropism. Columns 1-2. The reference teaches that useful retroviral particles may encode the chimeric envelope protein (col. 1, lines 58-63, and col. 6, lines 27-30) as well as including desirable heterologous genes (i.e. therapeutic genes- column 6, lines 46-65).

Applicants respectfully disagree and traverse below. Claims 9-11, 13-15 and 39 depend from either amended claim 7 or 8. Claim 11 has been canceled.

As set forth above, Kingsman fails to teach the recited nucleic acid molecule and vector. Therefore, the Office has not demonstrated a *prima facie* case of obviousness. Even assuming that the Office could present such a case, the fact that Kingsman discloses only viruses expressing chimeric MLV envelope proteins that are capable of infecting mouse cells is sufficient evidence of "teaching away" from the claimed invention to overcome the *prima facie* case of obviousness. In addition, applicants' surprising results, in light of what is described in Kingsman, provide additional evidence of non-obviousness. The Office has not pointed to anything in Anderson that remedies these deficiencies of Kingsman.

Accordingly, skilled practitioners, reading Kingsman and Anderson, individually or in combination, would not have been led to make or use applicants' nucleic acid molecules or vectors. Thus, the claimed invention would not have been obvious over any combination of Kingsman and Anderson, and withdrawal of this rejection is respectfully requested.

The Office also rejected claims 9-15 as allegedly obvious over Kingsman in view of U.S. Pat. No. 5,736,387 ("Paul") and Panda et al., Virology 273:90-100 ("Panda"). The Office states (at pages 9-10):

> ... [Paul] also indicates that it may be useful to modify the retroviral vectors such that they are no longer capable of infecting the cells expressing the wild-type viral envelope protein receptor. Column 18. The reference teaches that one means for accomplishing this is to inert a mutation disrupting the ability of the protein to bind that native envelope protein receptor ... Such mutations for the MuLV envelope protein are disclosed in the art. See e.g.. Panda, pages 90 and 95.

Applicants disagree. Claims 9-15 depend from claim 7 or 8, which have been amended as set forth above. Claims 11 and 16 have been canceled.

The deficiencies of Kingsman are as discussed above. Paul fails to rectify these deficiencies. Paul does not disclose any nucleic acid molecules or vectors encoding chimeric envelope proteins such that retroviral particles expressing the chimeric envelope proteins are capable of infecting human cells, but not mouse cells. In fact, Paul only discloses viruses that infect mouse cells (see, e.g., Examples 5 and 8). Neither does Panda remedy the deficiencies of Kingsman. Panda discloses nucleic acid sequences having point mutations that encode severely defective MLV envelope proteins (see the Abstract). There is nothing in the reference to suggest chimeric MLV envelope proteins that can render viruses expressing them capable of infecting human cells. Thus, nothing in Kingsman, Paul, or Panda, individually or in combination, would have led skilled practitioners to applicants' claimed nucleic acid molecules and vectors. As such, claims 9, 10, and 13-15, which recite these nucleic acid molecules and vectors, would not have been obvious over Kingsman, Paul, and Panda. Accordingly, applicants respectfully request that this rejection be withdrawn.

The Office next rejected claim 38 as allegedly obvious over Wu in view of Yamada et al., Biochemistry 33: 11678-83 ("Yamada") and US 2002/0081280 ("Curiel"). Applicants do not agree with this rejection. However, for the purpose of expediting prosecution of this application, claim 38 has been canceled, rendering the rejection moot.

New claims 45-50

New claims 45-50 recite an isolated nucleic acid molecule or a vector comprising a nucleic acid sequence encoding a chimeric retrovirus envelope protein comprising a Murine Leukemia Virus (MLV) ecotropic envelope protein and a human epidermal growth factor receptor (HRG) ligand inserted within the extracellular domain (SU) of the MLV ecotropic envelope protein, such that a retroviral particle comprising the chimeric retrovirus envelope protein is capable of infecting a human cell. Applicants submit that none of the references cited

in this Office Action discloses such nucleic acid molecule or vector. Further, applicants submit that skilled practitioners, reading these references, individually or in combination, would not have been led to such nucleic acid molecule or vector.

CONCLUSION

Applicants respectfully submit that all pending claims are in condition for allowance, which action is expeditiously requested. Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims. The fee in the total amount of $60 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No.: 07917-166US1 .

Respectfully submitted,

Date: 2/12/08

J. Peter Fasse
Reg. No. 32,983

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

21852381.doc